Lung Cancer in HIV-Positive Patients

Suchita Pakkala, MD, and Suresh S. Ramalingam, MD

Abstract: Malignancies account for more than a third of all deaths in human immunodeficiency virus (HIV)-positive patients. Although acquired immunodeficiency syndrome-related mortality is decreasing with the introduction of effective antiretroviral therapy, the incidence of lung cancer in patients with HIV remains high. Lung cancer has now become the leading cause of mortality among the nonacquired immunodeficiency syndrome defining malignancies. Within the HIV population, the incidence of lung cancer is estimated to be approximately 2 to 4 times that of the general population. Often these patients present with advanced disease (stage III or IV) at a younger age and have an inferior overall survival, when compared with non-HIV patients. Development of lung cancer in patients with HIV has been linked to various factors including immunosuppression, CD4 count, viral load, and smoking. This article reviews the impact of HIV on the incidence, risk factors, clinical presentation, and treatment of lung cancer.

Key Words: Lung cancer, HIV, AIDS, Antiretroviral therapy, NSCLC.

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The acquired immunodeficiency syndrome (AIDS) epidemic began in 1981 with reports of previously healthy males developing diseases that had otherwise been limited to immunocompromised patients. Among the diseases reported, certain cancers, specifically Kaposi sarcoma (KS) quickly emerged as having an association with the newly described acquired immunodeficiency syndrome.[1] Since those early days, similar associations have been seen with non-Hodgkin lymphoma and cervical cancer. According to current Centers for Disease Control (CDC) guidelines, these three cancers are now described as AIDS defining cancers (ADCs).[2] In 1996, with the introduction of highly active antiretroviral therapy (HAART), the incidence of KS and non-Hodgkin lymphoma decreased significantly mirroring the decrease seen in AIDS-related morbidity and mortality.[3–12]

Department of Hematology and Medical Oncology, Emory University School of Medicine, Winship Cancer Institute, Atlanta, Georgia.
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Address for correspondence: Suresh S. Ramalingam, MD, 1365 Clifton Road NE, Rm C-3090, Atlanta, GA 30322. E-mail: suresh.ramalingam@emory.edu
Dr. Ramalingam is a Distinguished Cancer Scholar of the Georgia Cancer Coalition.

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In the pre-HAART era, the non-AIDS defining cancers (NADCs) such as lung cancer only accounted for an estimated 10 to 20% of all cancers in the human immunodeficiency virus (HIV) population. Nevertheless, as AIDS-related illnesses declined, the proportion of NADCs has more than doubled in the post-HAART era.[5–7,13] A recent study demonstrated a significant increase in the proportion of NADC from 20% in the pre-HAART era to 71% of all cancers in the modern era (2001–2006).[6]

Together, ADCs and NADCs account for up to a third of all deaths in HIV-positive patients.[14] The shift in incidence that accompanied the use of HAART has also impacted mortality, making NADCs one of the leading causes of death with lung cancer being the most fatal.[14–20]

Although lung cancer is the most common and deadliest cancer worldwide,[21] it disproportionately affects HIV-positive patients resulting in a higher incidence and a worse prognosis, when compared with the general population.[7–10,22–48]

INCIDENCE

Early in the AIDS epidemic, several case reports noted the occurrence of lung cancer in HIV-positive patients younger than 40 years.[49,50] This raised the question of whether HIV-infected patients are at a higher risk for developing lung cancer. Many studies have compared the incidence of lung cancer cases in patients with HIV to the general population by calculating age- and sex-adjusted standardized incidence ratios (SIRs). SIR is an estimate of the ratio of the incidence of cancer in a given patient subset compared with the projected cancer incidence in the population at large. For instance, an SIR of >1 would indicate that lung cancer occurs more frequently in HIV-infected patients than in the general population. Some studies have used incidence rates to describe the number of new cases per persons at risk within a given time.

Pre-HAART Era

Studies in the pre-HAART era demonstrated a wide variability in lung cancer incidence with SIRs as high as 6.5 (confidence interval [CI]: 4.5–8.9),[34,39] whereas others failed to demonstrate any elevations at all[51–53] (Table 1). Many of these studies are limited by small patient numbers, especially in an era when AIDS-related illnesses predominated over non-AIDS-related illnesses. The largest study to examine this issue comprised 302,834 patients with AIDS in 11 US regions from 1978 to 1996. It demonstrated that lung cancer (n = 808) was the most commonly diagnosed NADC with a SIR of 4.5 (95% CI: 4.2–4.8).[36] Further analysis of this Match registry also showed that lung cancer incidence rose as the AIDS epidemic progressed (SIR of 2.5 [95% CI: 1.9–3.3]

TABLE 1. Lung Cancer Incidence

Study	Location	Period	Lung Cancer/ HIV Population	Overall SIR (CI)	Pre-HAART		HAART		Late Post-HAART	
					SIR (yr)	CI	SIR (yr)	CI	SIR (yr)	CI
Koblin et al.[52]	US: NY, SF	1978–1990	20/15,565		0.6	0.4–2.8				
Grulich et al.[34]	Australia	1980–1993	6/3616		3.8	1.39–8.29				
Gallagher et al.[44]	US: NY	1981–1994	217/122,993		3.3	2.86–3.75				
Cooksley et al.[53]	US: Texas	1974–1994	18/14,986		0.6	0.03–1				
Frisch et al.[36]	US: 11 areas	1978–1996	808/302,834		4.5	4.2–4.8				
Parker et al.[39]	US: Texas	1990–1995	36/26,181		6.5	4.5–8.9				
Grulich et al.[31]	Australia	1985–1999	17/13,067	1.4 (0.84–2.30)						
Herida et al.[30]	France	1992–1999	99/77,025		1.13	0.71–1.72	2.12	1.67–2.65		
Hessol et al.[57]	US: SF	1990–2000	86/14,210	2.6 (2.1–3.2)						
Bower et al.[47]	England	1986–2001	11/8400		0.8/10,000	0.2–3.2	6.7/10,000	3.1–13.9		
Engels et al.[7]	US: 11 areas	1980–2002	393/375,933		2.5 (80–89) 3.3 (90–95)	1.9–3.3 2.9–3.8	2.6	2.1–3.1		
Engels et al.[37a]	US: Hopkins	1989–2003	33/5238	4.7 (3.2–6.5)	1.7	0.2–6.3	5.2 (95–99)	2.8–8.7	5.3 (00–03)	3.1–8.4
Clifford et al.[10]	Switzerland	1985–2003	14/7304	3.2 (1.7–5.4)						
Dal Maso et al.[32]	Italy	1986–2004	54/21,951		2.1	1.2–3.3	4.1 (97–04)	2.9–5.5		
Patel et al.[9]	US: 13 areas	1992–2003	140/54,780	3.3 (2.8–3.9)	3.5	2.5–4.9	3.8 (96–99)	2.8–5	3.6 (00–03)	2.8–4.6
Powles et al.[35]	Europe	1983–2007	18/11,112	1.95 (1.16–3.1)	0	0–1.52	3.1 (96–01)	1.34–6.11	2.37 (02–07)	1.14–4.36
Bedimo et al.[28]	US: VA System	1997–2004	504/33,420				2[b]	1.8–2.2		
Long et al.[8a]	US: Hopkins	1996–2005	29/2566				5.5	3.7–8		
Guiguet et al.[27]	France	1998–2006	207/52,278	1.73			0.85/1000	0.74–0.97		
Silverberg et al.[45b]	US: Kaiser	1996–2007	54/20,227	1.9 (1.4–2.5)			3.9 (96–99)	2.1–7.1	1.1 (00–03) 2.1 (04–07)	0.6–1.9 1.4–3.2

[a] Compared with Urban population.
[b] Compared with HIV negative cohort.
US, the United States; HIV, human immunodeficiency virus; SIR, standardized incidence ratio; CI, confidence interval; HAART, highly active antiretroviral therapy; VA, Veteran's Administration.

in 1980–1989 versus 3.3 [95% CI: 2.9–3.8] in 1990–1995).[7,54] Other large US studies substantiated the findings of the Match database with lung cancer SIRs of 3.3 (95% CI: 2.8–3.9) (1981–1994) and 3.5 (95% CI: 2.9–3.8) (1992–1995) among HIV-infected people.[9,44] In contrast to larger US studies, most European studies demonstrated SIRs that did not exceed 1.13 before HAART,[30,35,47] although this finding was not consistent across Europe.[32,38]

Post-HAART Trends

Despite the use of antiretroviral (ARV) therapy, HIV-infected patients remain at higher risk for developing lung cancer than their non-HIV counterparts as evident by SIRs that range from 2 to 6 (Table 1).[7–9,28,30,35,37,38] Patel et al. investigated lung cancer trends in 54,780 patients with HIV from 1992 to 2003 by examining the incidence rates and SIRs of two large US multicenter prospective cohorts: Adult and Adolescent Spectrum of HIV Disease (ASD) and HIV Outpatient Study (HOPS). During this period, a total of 140 patients developed lung cancer with an incidence rate that peaked in 1996 and a SIR of 3.3 (95% CI: 2.8–3.9).[9] Overall, there was a nonsignificant upward trend in the incidence rate that was also described in other separate single institution

studies.[8,37] Although crude incidence rates seem to be increasing with HAART, an Italian study noted that rates are tempered when adjusted for age.[55] In contrast, lung cancer incidence has significantly declined in the general population over this time period.[9] Hence, when comparing the incidence in HIV-infected patients to the general population, Patel et al.[9] noted no consistent trends except that the standardized rate ratio peaked at 3.8 with early HAART use. Therefore, since HAART, crude incidence rates for lung cancer appear to be rising likely as a consequence of an increasing HIV prevalence and an aging population. Nevertheless, there is some evidence to suggest that the use of HAART is accompanied by a decrease in SIRs.

The Match database demonstrated a similar SIR pattern from 1992 to 2002, but the peak in incidence occurred earlier in 1994.[7] This slightly earlier peak in incidence may be explained by the fact that the Match registry is an AIDS registry, and the incidence of AIDS peaked around 1993 after the CDC broadened the definition.[2] Furthermore, unlike in the pre-HAART era, these trends do not seem to be limited to the United States. In a European study of 11,112 HIV-positive patients, the SIR peaked at 3.1 in 1996–2001 but subsequently fell to 2.27 in 2002–2007.[35] Extended follow-up in the post-HAART era has shown that although lung cancer rates have declined, the incidence remains elevated.

Impact of ARV Therapy

A meta-analysis of 847 lung cancer cases illustrated that the availability of HAART did not significantly alter lung cancer incidence which remained elevated.[33] Another study examined 96,000 HIV-positive patients in 19 North American cohorts from 1988 to 2007 and found that lung cancer incidence has not changed.[56] Nevertheless, most studies have examined the effect of periods (e.g., pre-HAART and post-HAART) on the incidence of NADCs rather than the actual impact of HAART itself making it is difficult to derive definitive conclusions about whether ARV therapy affects the incidence of lung cancer. To assess the impact of ARV therapy directly, smaller studies have compared those treated with HAART with those who were not and found conflicting evidence regarding whether HAART lowered the risk of lung cancer[10,57] or increased it.[58,59] The larger ASD/HOPS database analysis concluded that the incidence of lung cancer did significantly decrease with ARV therapy use.[9] Nevertheless, a French analysis of the large FHDH-ANRS CO4 (French Hospital Database on HIV) prospective cohort did not find a correlation between exposure or duration of antiretroviral therapy (ART) and lung cancer, although CD4 count at cancer diagnosis seemed to be related.[27] The international SMART trial specifically evaluated the use of intermittent ARV therapy for CD4 count <250 or until count >350 versus continuous ARV therapy to maintain viral suppression.[60] The results indicated a threefold increased risk of lung cancer in the intermittent arm compared with the continuous ARV therapy arm. Nevertheless, this difference was not significant, and numbers of events were small ($n = 8$). Hence, it seems that the use of ART alone may not be as important as the target CD4 count.

RISK FACTORS

Behavioral Factors (Smoking and Intravenous Drug Use)

As expected, cigarette smoking is an independent risk factor for the development of lung cancer in HIV-positive individuals.[27,61] It is estimated that 51% of patients with HIV have smoked cigarettes.[62,63] The propensity of HIV-infected patients to develop lung cancer is often attributed to the fact that smoking is 2 to 3 times more common than in the general population with rates reported as high as 85 to 100% in larger series.[25,26,37,42,46,59,64,65] This was reinforced by a report in which none of the 865 nonsmoking HIV-positive individuals developed lung cancer.[10] Furthermore, among those who died of respiratory cancer, up to 96% were smokers, which strongly correlated with patient mortality.[14,59]

Parker et al.[39] estimated that smoking alone could not account for the increased risk of lung cancer. For example, a 20 to 35 pack-year smoking history has been associated with lung cancer in patients with HIV, which by comparison is often significantly less or at least equivalent to control subjects in case series.[25,41–43,46] One study illustrated that despite adjusting for smoking, the risk for lung cancer remained elevated with a SIR of 2.5 (95% CI: 1.6–3.5) and did not normalize even when assuming all patients with HIV were smokers or by doubling the smoking rate (SIR 1.7 and 2.4, respectively).[37] Although previous reports were limited by incomplete smoking histories, Kirk et al.[59] showed that individuals matched for age, sex, and smoking were still 3.6 times more likely to die of lung cancer in HIV-infected than noninfected people. Examination of 3707 HIV-positive veterans verified that irrespective of smoking, the risk of lung cancer was almost double that of the 9890 HIV-negative matched controls.[66] Nevertheless, in a multivariate analysis, smoking was associated with a much greater risk than HIV alone (relative risk of 9.8 [95% CI: 4.44–21.4] versus 1.8 [95% CI: 1.28–2.15]).

In addition to smoking itself, several reports have indicated that intravenous drug users are at a higher risk for developing lung cancer.[10,25,30,32,44,67] Nevertheless, this is not consistent across studies, and the results may be confounded by high rates of smoking among intravenous drug users.[10,32,37,59,64]

Role of Immunodeficiency

Evaluation of the risk of lung cancer in transplant recipients has further shifted the emphasis from lifestyle-related risk factors to immunosuppression itself. Although behavioral risk factors differ between patients with HIV/AIDS and transplant patients, a large meta-analysis of 12 studies revealed that the higher risk for lung cancer was comparable between patients with HIV/AIDS (SIR of 2.7 [95% CI: 1.91–3.87]) and organ transplant recipients that received immunosuppressive therapy (SIR of 2.18 [95% CI: 1.85–2.57]).[68] Additionally, a large meta-analysis has shown that the risk of lung cancer is higher in patients who developed AIDS,[33] whereas several other studies have demonstrated a temporal association with the onset of AIDS.[31,32,34,36,44,67] The largest study to evaluate this associ-

ation examined 1489 lung cancer cases among 397,927 patients with AIDS from 1980 to 2002 and showed a markedly elevated SIR of 10.5 at the time of AIDS onset (6 months before 3 months after) and a significant upward trend in SIRs during the other periods from 60 months (SIR of 1) before 60 months after (SIR of 2.9) AIDS diagnosis.[54] Nevertheless, it is also plausible that that the higher incidence of lung cancer might be secondary to closer surveillance of patients with AIDS.

Unlike ADCs, the risk for lung cancer does not seem to be directly correlated to CD4 count.[7,10,25,28,37,42,54,59,69,70] In fact, the median CD4 count at diagnosis for NADCs is often significantly higher than that reported with ADCs[5,6,8,13,14,18] and for lung cancer, the CD4 count ranges from 121 to 364.[25,26,28,42,46,48,70] Although CD4 count does not seem to have a linear relationship with lung cancer incidence, Guiguet et al.[27] demonstrated that the rate of lung cancer doubled as patient's CD4 count decreased from >500 to 350–499 and continued to increase as CD4 counts declined. This French Hospital Database on HIV (FHDH-ANRS CO4) cohort also demonstrated that a recent low CD4 count predicted cancer risk irrespective of duration. Silverberg et al.[71] examined 19,280 HIV-infected US Kaiser patients in the post-HAART era and showed that lung cancer was only elevated in those with CD4 counts <200. In addition to predicting risk, CD4 count may also be related to lung cancer severity as implied by Brock et al.[25] who noted a slight inverse correlation of various CD4 count ranges to advanced stage cancer. These studies reinforce the importance of immunosuppression as indirectly measured by CD4 count.

Given that many factors result in the variability of CD4 counts, CD4 nadir is often used as a surrogate marker for immunodeficiency. Several small reports have failed to demonstrate a significant association between CD4 nadir and lung cancer incidence, although one study did suggest a positive trend.[35,37] This association proved to be significant in the larger ASD/HOPS database analysis[9] but not predictive in the FHDH-ANRS CO4 cohort. Therefore, it is clear that patients with HIV/AIDS are at higher risk for developing lung cancer and that immunosuppression itself is a risk factor, although the exact role of immunodeficiency remains to be elucidated.

Potential Viral Oncogenesis

HIV itself has been implicated as a potential cause for oncogenesis. Specifically, evidence suggests that the Tat protein required for viral replication may also affect genes involved in controlling cellular proliferation.[72] Nevertheless, studies have not discovered a link between HIV viral load and lung cancer occurrence.[37,59] An analysis of 92 patients with HIV with lung cancer indicated that viral load may be linked to lung cancer severity,[25] but this was inconsistent with the fact that 63% of HIV-infected patients who died of lung cancer had RNA levels <500.[14]

Other viruses have been investigated in an attempt to account for the elevated lung cancer risk in the setting of moderate immunosuppression. Stebbing et al.[73] found no evidence of KS-associated herpes virus or any of the cancer-associated human polyomaviruses in the tumor samples of HIV-related lung cancer. On the other hand, human papillomavirus (HPV) DNA has been found in about 25% of all lung cancer cases with regional distributions higher in Asian compared with western populations.[74] HPV 16 and 18 E6 oncoproteins have also been linked to nonsmoking females with adenocarcinoma histology.[75,76] Nevertheless, studies have failed to reveal a causal relationship between HPV and lung cancer in general.

CLINICAL MANIFESTATIONS

Demographics

Lung cancer in HIV-positive individuals disproportionately affects younger patients with a median age that range from 38 to 49 years, significantly less than controls (46 versus 64 years) (Table 2).[22,24,25,39,41,42,46,49,65,67,77] As expected with most cancers, the risk of lung cancer increases with age.[25,37] Thus, the post-HAART shift in age distribution toward middle aged patients with AIDS places this group at a higher risk for lung cancer.[55] Historically, men have the highest risk for lung cancer, which likely reflected the male predominance seen in the HIV population and among smokers.[63] With increasing prevalence of HIV, lung cancer that occurred almost exclusively (90% of cases) in men is now being diagnosed in women in up to a third of all cases.[37,70,78] HIV-infected women are not only at increased risk for lung cancer but also seem to have higher SIRs than male counterparts based on several studies.[32,33,36,44,67] Nevertheless, a recent study implies that women are at higher risk of developing lung cancer irrespective of HIV status.[61] Similar to gender, the proportion of African Americans infected with HIV is on the rise, ultimately altering the demographics of the at risk population in the United States.[25,79]

Clinical Presentation

Although the characterization of lung cancer in patients with HIV is limited to small case series, two reports described cough, weight loss, and dyspnea as the most common symptoms. Other symptoms typically observed were fever, night sweats, chest pain, and anorexia.[42,43] HIV-infected patients were more likely to be symptomatic than controls and often presented with tachypnea, cachexia, tachycardia, and fever. No significant difference in blood counts were detected.[43] Radiographically, patients presented with peripherally located masses and infiltrates (29/41), often involving the upper lobes (27/29 of peripheral tumors). Adenopathy occurred in about half of patients, whereas effusions occurred in about one third.[43,65,80]

The most common histologic diagnosis is adenocarcinoma (34–67%) followed by squamous cell (17–39%), large cell (3–16%), and bronchoalveolar (2–3%) cancer in HIV-positive patients. Non-small cell lung cancer represents 67 to 86% of primary lung cancers in patients with HIV; small cell lung cancer comprises another 6 to 14% with unidentified subtypes accounting for the remaining percentage.[22,24–26,37,54,65] The majority of patients present with either advanced stage III (18–29%) or IV (50–68%) disease.[25,26,54,65] Histology and stage distribution in HIV-positive patients were comparable with non-HIV controls in two studies[26,42]; however, a larger contemporary study confirmed prior observations that a significantly higher

TABLE 2. Patient Characteristics

	Sridhar et al.[42]	Vyzula et al.[46]	Tirelli et al.[26]	Alshafie et al.[23]	Spano et al.[48]	Brock et al.[25]	Lavole et al.[24]	Bertolaccini et al.[22]
Patients (*n*)	19	16	36	11	22	92	49	26
Years	86–91	88–95	86–98	90–94	93–02	86–04	96–07	03–07
Median age (yr)	47	45	38	50	45	46	46	39
Males (%)	100	94	89	82	86	67	86	85
Race, W/B (%)	63/21	—	—	0/91	—	21/79	94/—	—
Smoking (%)	94	100	94	90	95	99	100	85
Median pack-years	60	30	40		40	30	31	30
IVDU (%)	21	63	69	81	23	58	17	58
Homosexual (%)	32	38	17	0	45	—	18	23
Adenocarcinoma (%)	42	50	36	46	36	48	67	—
Squamous cell (%)	31	19	33	36	50	17	17	—
Large cell (%)	11	19	14	9	5	5	17	—
Small cell (%)	5	12	14	0	5	9	—	19
Other (%)	11	—	3	9	5	21	—	—
Median CD4	121	184	150	329	364	305	350	143
CD4 <200 (%)	53	54	44	30	9	—	—	—
Latency (yr)						5.5	8.6	—
PS <2 (%)	37	69	43	—	69	—	71	—
Stage III/IV (%)	79	81	84	90	75	87	84	76
Median survival (mo)	3	5.4	5	3	7	6.3	8.1	23

IVDU, intravenous drug user; PS, performance status.

percentage of patients with HIV presented with more advanced stage lung cancer.[25]

TREATMENT AND PROGNOSIS

Data on lung cancer treatment in HIV-infected patients are also largely limited to case descriptions. About one fourth of patients with HIV did not receive lung cancer directed therapy in a large US case series during the pre and HAART era as opposed to 12% in a post-HAART French study.[24,25] In both instances, poor performance status was the primary reason that patient's were not treated. HIV-infected patients are less likely to undergo curative surgery than noninfected patients mainly due to advanced stage.[25] Nevertheless, two thirds of HIV-positive patients in three separate studies were deemed ineligible for surgery based on poor performance status or prior pulmonary infections.[22,26,81] Massera et al.[82] reported successful surgical resection with no major complications in two patients with CD4 <200. The advent of HAART did not seem to increase the percentage (13% versus 15%) of patients that were eligible for curative surgery.[25] Those who were not surgical candidates were mainly treated with radiation alone (39%) and to a lesser extent, chemotherapy (10%) or combined modality treatments (13%). This differed vastly from a French study in which all nonsurgical patients received either chemotherapy (63%) or chemoradiation (12%).[24] Among the 74 patients with HIV treated in various post-HAART studies, only three suffered from treatment-related deaths, whereas the majority still died as a result of their cancer.[22,24,83] Opportunistic infections occurred in 8 of 25 patients treated with systemic chemotherapy, but this likely represents the added complication of advanced immunosuppression because the median CD4 count was 150.[26] On the other hand, despite presenting with a poor performance status and approximately 50% developing grade 3 or 4 hematologic toxicities, HIV-infected patients received a similar number of chemotherapy cycles with equivalent outcomes to HIV-negative controls in the modern era.[83] Additionally, none of the patients treated with systemic chemotherapy in the post-HAART era died of an opportunistic infection arguing against withholding treatment on the basis of immunodeficiency alone.[24,83] With the use of thoracic radiotherapy, esophagitis has been noted to be the most common adverse event, similar to non-HIV patients.[24,26] An additional complicating factor in the treatment of patients with HIV with lung cancer is the potential interaction of ART with chemotherapy that has yet to be fully defined.[84]

Lung cancer represents 5% of all deaths and 15% of all cancer deaths in the HIV population.[14] Traditionally, patients with lung cancer and HIV disease experience a shorter median survival of only 3 to 9 months and have a poor overall prognosis.[8,25,26,41,43,46,85] In a study by Sridhar et al.,[42] the median survival was 3 months for HIV-infected patients with lung cancer, compared with 10 months in a matched non-HIV control group. Notably, none of the patients in the HIV cohort survived beyond 1 year. Mortality in this population has been associated with African American race and advanced stage at lung cancer diagnosis, which did not differ by HIV status in a multivariate analysis.[25] Favorable prognostic factors include early-stage disease, good performance status, and the use of HAART.[24] Survival by stage seems to be equivalent to non-HIV patients implying that patient with HIV mortality

maybe worse due to higher proportion of patients with advanced disease.[25,83]

More encouraging survival results were noted by Bertolaccini et al.[22] who demonstrated a median survival of 23 months in HIV-infected patients with lung cancer who received anticancer therapy. The 4-year survival rate was 54%. Nevertheless, larger comparable studies have indicated that the overall survival still remains poor ranging from 6.3 to 8.1 months in the HAART era.[24,25,48] Poorer mortality outcomes may be in part related to patients not receiving appropriate therapy, but this does not explain why mortality in surgically treated patients with HIV was twice that of matched controls when perioperative factors did not play a role.[86]

FUTURE DIRECTIONS

The landscape of HIV has changed dramatically since the institution of HAART. As AIDS-related illnesses decline, lung cancer has emerged as a significant cause of morbidity and one of the leading causes of mortality. HIV-infected patients are at least 2 to 3 times more likely to develop lung cancer than the general population. Immunodeficiency especially CD4 counts <500 seems to place HIV-infected individuals at a higher risk, but the development of lung cancer itself does not seem to be directly related to absolute CD4 count.[27,87] Rather, CD4 count at cancer diagnosis with its inherent variability seems to be a measure of the degree of immunosuppression. Although the use of ART itself may not clearly decrease the risk of lung cancer in this population, it is already known that cancer risk and general mortality in ARV therapy-treated individuals with CD4 counts >500 approaches that of the general population.[88,89] Therefore, the current available evidence supports the idea that targeting a higher CD4 count with therapy may have some beneficial effects in preventing lung cancer.

Smoking is clearly associated with the risk of lung cancer and seems to have a greater impact within the HIV population compared with the general population. Therefore, strategies to decrease the smoking prevalence are of great importance. In addition, persistent pulmonary complaints or radiologic abnormalities in the chest should be aggressively pursued. Lung cancer screening has not demonstrated a mortality benefit in the general population, but studies are ongoing, and data in patients with HIV are lacking. Although screening CTs have not yet become the standard of care in this high-risk smoking population, one must take note that 60% of HIV-positive patients had chest x-rays that were negative for malignancy within a year of diagnosis.[25,90]

Patients with HIV with lung cancer seem to have a more aggressive presentation and a poorer prognosis compared with the general population. This may be in part due to a reluctance or inability to treat patients who are chronically ill and immunosuppressed. Nevertheless, it seems that patients who are treated do benefit from improved outcomes with tolerable side effects. Although these studies are often small case reports that introduce an underlying bias. There is limited evidence to guide lung cancer therapy for these patients, and more prospective studies are needed. Further characterization of the disease may help guide targeted therapies that can potentially treat patients with fewer toxicities. Future studies should focus on understanding the prevalence of molecular abnormalities such as epidermal growth factor receptor mutation, Kirsten rat sarcoma mutation, and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase translocation. This might lead to the development of tailored therapeutic options for patients with HIV with lung cancer.

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